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DATE MAILED: 02/15/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 4/18/94+5/17/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 22 and 24-32 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-21 and 23 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 22 and 24-32 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

Claims 22 and 24-32 are pending in the instant application with claims 1-21 and 23 canceled by amendments filed in Papers No. 2, 3, and 9.

Claims 22 and 24-32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,722,848 in view of Mackett et al., reference AX; Smith et al., reference BT; Weir et al., Proc. Natl. Acad. Sci. USA 79:1210 (1982); Mackett et al., Abstract from Pox-Iridovirus Meeting, Cold Spring Harbor, Sept. 20-23 (1982) p. 54; or Panicali et al., Abstract from Pox-Iridovirus Meeting, Cold Spring Harbor, Sept. 20-23 (1982) p. 55. The cited references each teach the use of a recombinant vaccinia virus as an expression vector for eucaryotic cells. Mackett et al. and Smith et al. teach a method of producing proteins comprising transfecting eucaryotic cells with recombinant vaccinia viruses comprising a DNA sequence encoding heterologous proteins. Accordingly, it would have been obvious to one skilled in the art to employ the recombinant vaccinia viruses used to amplify the production of proteins in an animal host as taught in U.S. Patent No. 4,722,848 to produce said proteins in eucaryotic host cells *in vitro* as taught by the cited references.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 U.S.P.Q. 619 (C.C.P.A. 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

Applicants argue that the cited references do not constitute prior art in the '330, '112, and '848 patents and, therefore, the double patenting rejection should be withdrawn. This argument has been considered, but is not persuasive. The subject matter of the three patents has been carefully studied; however, for the reasons set forth below, they fail to provide an adequate written description of the invention as now claimed. Accordingly, applicants are not being accorded the benefit of the earlier filing dates.

The amendment filed May 17, 1994 in Paper No. 13 is objected to under 35 U.S.C. § 132 because it introduces new matter into the specification. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the substitution of the abstract with: "Disclosed is a method for producing a protein involving infecting a culture of eucaryotic cells with a recombinant vaccinia virus."

Applicant is required to cancel the new matter in the response to this Office action.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, fails to provide an adequate written description of the invention as now claimed.

The specification, as originally filed, fails to provide an adequate written description of a method for producing a protein which comprises infecting a culture of eukaryotic cells with a recombinant vaccinia virus synthetically modified by the presence, in a non-essential region of the vaccinia genome, of DNA not naturally occurring in vaccinia and coding for: (i) any protein, (ii) any enzyme, (iii) thymidine kinase, (iv) any glycoprotein, (v) a herpes simplex glycoprotein, (vi) influenza virus hemagglutinin, (vii) any antigen, or (viii) hepatitis B virus surface antigen, under conditions suitable to allow expression of the protein, and isolating the expressed protein from the cell culture. Applicants must indicate the region(s) of the specification which support the claims as none are apparent to the Examiner.

Claims 22 and 24-32 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Applicants argue that the claims of the '112 patent disclose and enable the instant invention. This argument has been considered, but is not persuasive.

First, the claims in the '112 patent are product claims directed to some of the same recombinant vaccinia viruses as the instant claims; however, neither the claims or the specification teach a method of producing a protein which comprises infecting a culture of eucaryotic cells with said vaccinia viruses under conditions suitable to allow expression of the

proteins encoded therein and isolating the expressed protein from the cell culture. The phrase in claim 2, "wherein said DNA is expressed in a host by the production of protein," (1) does not porvide an adequate written description of a method of producing a protein, (2) is confusing because DNA is not expressed **by** the production of protein, expression of DNA **results in** the production of protein, (3) is directed to an animal host, and not a cultured eucaryotic cell, and (4) does not disclose the secretion of an expressed protein to the cell culture, e.g., the expressed protein could be intracellular, on the cell surface. To satisfy the written description requirement, "the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*, The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" See Vas-Cath v. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). [Emphasis in original.] Accordingly, because the '112 patent fails to provide an adequate written description of the invention as now claimed, applicants are not being accorded the benefit of the earlier filing date.

Second, with respect to applicants' enablement argument it is presumed that applicants intend that the parent application teaches "how to make" the instant invention. The issue in the rejection, *supra*, is not whether the parent, and instant, specifications enable the instant invention, but whether they provide an adequate written description of the claimed method as something applicants actually invention. The courts have held that "it is possible for a specification to *enable* the practice of an invention as broadly as it is claimed, and still not

describe that invention. See Vas-Cath v. Mahurkar, *supra*; In re DiLeone, 436 F.2d 1404, 168 U.S.P.Q. 592 (C.C.P.A. 1971). In the instant case, the parent specification fails to provide an adequate written description of the invention as now claimed. Rather, the subject matter of the instant claims was added to the specification in the amendment filed July 13, 1993 in Paper No. 9.

Applicants argue that the '848 and '587 patents provide a sufficient disclosure of the claimed invention as evidenced by claims 2-6 and claims 2-4, respectively. These arguments have been carefully considered, but are not persuasive.

First, in the '848 patent, the referenced claims are directed to a method of (i) amplifying a protein in a host animal and (ii) a method of immunizing a host animal. The claims of the '587 patent, like the claims of the '112 patent, are directed to some of the recombinant vaccinia viruses used in the instant methods. The claims in the '848 and '587 patents do not disclose, or provide an written description of, a method of producing a protein in cultures of eucaryotic cells or to the isolation of the expressed protein from the cell culture.

Applicants appear to acknowledge on p. 8, para. 1, of the Preliminary Amendment filed May 17, 1994 in Paper No. 13, that the '848, '112, and '578 patents only teach the recombinant vaccinia viruses and, thus, they urge that only the steps of infecting a culture of eucaryotic cells with the previously disclosed viruses and isolation of the expressed protein from the culture must be shown. This is not correct. The parent and, therefore, the present,

specifications must contain an adequate written description of the invention as a whole, in a manner that it reasonably convey to those skilled in the art that applicants contemplated the instant invention at the time the parent application was filed. In the instant case, claims have been presented which were not presented in the application when filed and the specification fails to provide adequate support for the newly added subject matter. Disclosure of different aspects of the invention, in different regions of the specification, is not sufficient to demonstrate that applicants actually were in possession of, or contemplated, the invention as now claimed, at the time the parent application was filed.

Applicants urge that the purpose of the infecting and isolating steps, be it for harvesting an expressed protein or detection of expression by the vaccinia virus is immaterial. Applicants further urge that the instant method was disclosed and enabled for either purpose, and that said method has utility. This argument has been considered, but is not persuasive.

First, as set forth above, enablement is **not** an issue in the instant written description rejection. Written description and enablement are two separate requirements set forth under 35 U.S.C. § 112, first paragraph. In the instant case, the parent specification fails to provide an adequate written description of the claimed methods of making a protein. In addition, utility is **not** an issue in the instant rejection.

Second, applicants' argument that disclosure of the method for any purpose is incorrect. The instant claims are means plus function claims; therefore, the specification must teach the method (means) in conjunction with the function (producing a protein which

can be isolated from the cell culture). See In re Donaldson Co., Inc., 29 U.S.P.Q.2d 1845 (Fed. Cir. 1994).

Applicants argue that Example XXXI and XXXII of the '848 specification which teach the expression of HBsAg and VP-11, respectively, in monolayers CV-1 cells and the detection of the expressed protein in the cellular supernatant "fully discloses and enables a method of infecting a culture of eukaryotic cells with recombinant vaccinia virus synthetically modified by the presence, in a non-essential region of the vaccinia genome, of DNA not naturally occurring in vaccinia and coding for the protein, under condition [sic] suitable to allow expression of the protein, and isolating the express protein from the cell culture." This argument has been carefully considered, but is not persuasive for several reasons.

First, the referenced region of the specification discloses the infection of *monolayers of CV-1 cells*, and does **not** provide an adequate written description of the infection of a *culture of eukaryotic cells*. Monolayers of cells are not equivalent to cultures of cells. Monolayers of cells are a single layer of cells which are plated in, or on, an agarose-based surface; whereas, cultures of cells describes a genus which includes, *inter alia*, liquid cultures. CV-1 cells are a species of eucaryotic cells, but are not equivalent to the genus of eucaryotic cells. In addition, the referenced regions of the specification discloses a DNA sequence encoding HBsAg and vP-11, and does **not** provide an adequate written description of a DNA sequence encoding any protein, any enzyme, thymidine kinase, any glycoprotein, herpes simplex virus glycoprotein, influenza virus hemagglutinin, or any antigen. Further,

the examples fail to teach the isolation of the expressed protein from the cell culture. In Example XXXI, the cultural supernatant was assayed for the presence of HBsAg with antibodies, however, the example does not teach the isolation of the protein. In Example XXXII, the infected CV-1 cells were lysed, centrifuged briefly to remove large cellular debris, and the supernatant was centrifuged for 18 hours at 30,000 rpm. The second centrifugation step results in the pelleting of aggregated HBsAg, cellular organelles, and virus particles. Note col. 57, lines 43-44 teaches that 10^8 pfu (plaque forming units; i.e., purified viral particles) presumably derived from the centrifugation procedure were used to immunize the rabbits, not μg of purified protein. The disclosure of a single species does not provide an adequate written description of the instant genus claims. See In re Smith, 458 F.2d 1389, 173 U.S.P.Q. 679 (C.C.P.A. 1972). Nor are there any teachings in the referenced regions of the specification that applicants contemplated the instant genus claims at the time the parent application was filed. Accordingly, the rejection is deemed proper and is maintained.

Applicants contention that Example XVII of the '848 and '112 patents which teaches the infection of BHK-21 and CV-1 monolayers with recombinant vaccinia virus comprising the DNA sequence encoding the HA gene and the *in situ* binding of antibody to the cells in said monolayers as evidenced by autoradiography, discloses the isolation of the expressed protein from the infected culture of cells is erroneous. The binding of antibody *to a layer of cells in nutrient agar* is **not** an adequate written description of the isolation of a protein *from the cell culture*. An autoradiograph is a means of visualizing the location, or presence, of the

protein in, or on the surface of, the infected cells and not in the cell culture. Further, the example fails to provide an adequate written description of a method of producing a protein using a recombinant vaccinia virus which comprises a DNA sequence encoding any protein, any enzyme, thymidine kinase, any glycoprotein, herpes simplex virus glycoprotein, influenza virus hemagglutinin, any antigen, or HBsAg, and isolating the protein from the cell culture. That is, the example fails to demonstrate that applicants contemplated the general use of recombinant vaccinia virus as an expression vector for expressing any heterologous protein in cultures of eucaryotic cells and the subsequent isolation of said protein from the cell culture as their invention at the time the parent applications were filed. In addition, as set forth above, monolayers of CV-1 and BHK-21 cells fail to provide an adequate written description of the claimed genus, i.e., a culture of eucaryotic cells. Accordingly, the rejection is deemed proper and is maintained.

Applicants argue the general teachings in the '848 and '112 patents provide a "full, enabling disclosure" of the instant invention. As set forth above, enablement is not the issue in the instant rejection, written description is. "It is possible for a specification to *enable* the practice of an invention as broadly as it is claimed, and still not *describe* that invention." [Emphasis in original.] See Vas-Cath Inc. v. Mahurkar, *supra*; In re DiLeone, *supra*.

Applicants' arguments on p. 11 of the preliminary amendment as to Examples XXXI and XXXII of the '848 patent, as well as Example XVII of the '112 patent, have been addressed, *supra*.

Applicants argue that the '330 patent discloses, in col. 12 and Examples XI and XII, conditions suitable to allow expression of the protein. This argument and the referenced sections of the patent have been carefully considered, but are not deemed persuasive. Col. 12, line 22 discloses the insertion and expression of the HSV TK gene into a mutant vaccinia virus as providing a "powerful tool for discriminating between vaccinia virus mutants containing other exogenous genes whether present alone in the vaccinia genome or present therein in combination with the HSV TK gene." Note col. 12, lines 29-33. The methods disclosed (col. 12, line 51 *et seq.*) teach the infection of cell monolayers with mutated virus under "conditions promoting plaque formation, i.e., those promoting cell growth and virus replication." Col. 12 fails to provide an adequate written description of a method of producing a protein which comprises infecting a culture of eukaryotic cells with a recombinant vaccinia virus which comprises a DNA sequence encoding any protein, any enzyme, thymidine kinase, any glycoprotein, herpes simplex virus glycoprotein, influenza virus hemagglutinin, any antigen, or HBsAg and isolating the protein from the cell culture. Example XI provides more details of the actual techniques to be employed in detecting the HSV TK expression in the viral plaques. As set forth above, the presence of the protein in the plaques was visualized by an *in situ* assay. The specification discloses that plaques on the CV-1 monolayer which contained and expressed the HSV TK gene phosphorylate IDC and incorporate it into their DNA, rendering the DNA insoluble. The autoradiograph identified the positive plaques (an autoradiograph is not a means of, nor, in the instant case

did it demonstrate, isolating a protein from the cell culture) which were then twice plaque purified and selected and analyzed for the presence of the HSV TK gene by *in situ* DNA hybridization. See Example XII, col. 28, lines 34-44. Accordingly, contrary to applicants' assertion, the '330 patent fails to provide an adequate written description of the instant invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure.

Assuming arguendo, that the specification does teach the claimed methods of producing proteins in cultures of eucaryotic host cells transfected with recombinant vaccinia viruses which comprise the DNA sequences encoding said proteins and isolating the expressed proteins from the cell culture, the specification fails to provide an enabling disclosure of the subject matter of claims 22 and 24-31. It is well known in art that many factors affect the production of a heterologous protein in a eucaryotic cell. These include, *inter alia*, protein cytotoxicity, differences in post-translational modifications, changes in the three dimensional conformation, mRNA stability, the type of promoter, etc.. In view of the unpredictability of this art, the mere expression of three heterologous genes in cultures of eucaryotic cells is insufficient evidence to claim that all proteins, enzymes, glycoproteins, and antigens can be produced in eucaryotic cells transfected with a recombinant vaccinia virus which comprises the DNA sequence encoding these compounds. Accordingly, given the limited teachings of

the specification, and the unpredictable nature of gene expression, one skilled in the art cannot make and use the claimed invention, absent undue experimentation. See Ex parte Forman, 230 U.S.P.Q. 546 (Pat. Bd. Appl. & Interf. 1986); Ex parte Sudilovsky, 21 U.S.P.Q.2d 1702 (Pat. Bd. Appl. & Interf. 1991).

In addition, the specification fails to provide an enabling disclosure for one skilled in the art to isolate all the proteins encompassed by the claims. A recent publication, Bio Critical Synergy: The Biotechnology Industry and Intellectual Property Protection, Presentations of the Intellectual Property Committee of the Biotechnology Industry Organization at the October 17, 1994, Hearing of the U.S. Patent and Trademark Office, San Diego, CA teaches that as recently as 1994, "purification of any protein involves many steps which often must be practiced in a precise order and under specific conditions of time, temperature, volume, concentration, *etc.*. These steps are not self-evident, and vary radically from protein to protein. There are a literally infinite [number of] combinations of columns, gradients, gels, precipitants, centrifugations, all with buffers of varying pH, salt, buffers, concentrations of same, etc., to choose from. Until it has been done, and the protein described, there is little guidance as to which way to go." See p. 104. The publication further teaches that "[t]he requirements of purification vary so much from protein to protein, that the knowledge gained from purifying one protein can be useless in devising a protocol to purify another, and in fact a detergent or other element used successfully in one protocol can inactivate or destroy another protein. An assay for a protein doesn't tell the person skilled in

the art where to begin, or what steps to take." See p. 105. Accordingly, given the limited teachings of the specification, and the unpredictable nature of protein isolation, one skilled in the art can not make and use the invention as claimed, absent undue experimentation. See Ex parte Forman, *supra*; Ex parte Sudilovsky, *supra*.

Claims 22 and 24-32 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

It is noted that applicants failed to respond the rejection as to the unpredictable nature of the expression of the DNA sequence encoding any heterologous protein in an eucaryotic cell culture.

In view of counsel's assurances that the **parent** applications are enabled because timely deposits were made, i.e., in accordance with In re Lundak, 723 F.2d 1216, 227 U.S.P.Q. 90 (Fed. Cir. 1985), the deposit requirement has been withdrawn. Applicants are correct that a deposit can be made after the filing of an application. It was the Examiner's intent to caution applicants that in order to be accorded the benefit of a parent application, the parent must provide an adequate written description of the claimed invention as well as an enabling disclosure. In order for the parent application to be enabling, the deposits, in said parent, must have been in accordance with deposit regulations as interpreted by Lundak.

Claims 22 and 24-32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is vague and indefinite in the recitation of a "protein." It is not clear which proteins applicants intend. The claim is also vague and incomplete in the recitation of "isolating the expressed protein from the cell culture." It is not clear what isolation procedures applicants intend.

Claim 24 is vague and indefinite in the recitation of an "enzyme." It is not clear which enzymes applicants intend.

Claim 26 is vague and indefinite in the recitation of a "glycoprotein." It is not clear which glycoproteins applicants intend.

Claims 27 and 30 are vague and indefinite in the recitation of a glycoprotein and antigen which is a "herpes simplex glycoprotein". It is not clear which glycoproteins and antigens applicants intend. Applicants are advised that when two claims in an application are duplicates or else so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to reject the other as being a substantial duplicate of the allowed claim. M.P.E.P. §706.03(k). Therefore, should claim 27 be found allowable, the duplicate claim 30 will be rejected under 35 U.S.C. § 101.

Claims 28 and 31 are vague and indefinite in the recitation of a glycoprotein and an antigen which is an "influenza virus hemagglutinin". It is not clear which glycoproteins and antigens applicants intend. Note comments with respect to claims 27 and 30, *supra*.

Claim 29 is vague and indefinite in the recitation of an "antigen". It is not clear which antigens applicants intend.

Applicants argue that the because the claims of the '330, '112, '848, and '587 patents employ the terms "protein", "enzyme", "herpes simplex glycoprotein", "influenza virus hemagglutinin", and "antigen", these terms are clear and definite. In addition, applicants allege that one skilled in art at the time of filing the instant application understood what the terms meant. Finally, because the present invention is a "pioneer invention" applicants contend that they are entitled to broad claims. These arguments have been considered, but are not persuasive for several reasons.

First, the allowance of claims in other patent applications have no bearing on the instant application. The prosecution of each application is based on the facts of that case. Therefore, since applicants have failed to provide any reasons or evidence which support the assertion that these terms are clear and definite, the rejection is deemed proper and is maintained.

Second, the assertion as to what an artisan understood at the time of filing the parent application is merely a conclusory statement. This argument counsel is unsupported by

evidence or declarations by those skilled in the art. Counsel's arguments cannot take the place of objective evidence. See In re Langer, 503 F.2d 1380, 183 U.S.P.Q. 288 (C.C.P.A. 1974); In re Payne, 203 U.S.P.Q. 245 (C.C.P.A. 1979).

Third, the Examiner agrees with applicants that it is the courts who determine whether or not an invention is a "pioneer." Accordingly, it is inappropriate for the Examiner to address these remarks.

Applicants argue that the methods for isolating a protein from the cell culture are disclosed in the instant and parent applications. This argument has been addressed, *supra*. Briefly, the referenced sections of the parent and instant applications fail to teach the isolation of a protein from the cell culture. The methods disclosed teach the detection of HBsAg in the supernatant, and wash, of CV-1 monolayers using antibodies (Example XXXI), the pelleting of aggregated HBsAg mixed with cellular organelles, and viral particles (Example XXXII), the detection of HA in CV-1 and BHK-21 cell monolayers (i.e., the detection of HA in the stationary, plated cells and not isolation from the cell culture) (Example XVII), and the detection of HSV TK gene expression in CV-1 monolayers (again, the presence of HSV TK in the plated cells as a method of discriminating between vaccinia virus mutants, and not the isolation of from the cell culture) (Example XI).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22, 26, 28 and 31 are rejected under 35 U.S.C. § 102(b) as being anticipated by Smith et al. (reference BS).

Smith et al. teach a method of producing influenza virus hemagglutinin which comprises transfecting an eucaryotic cell culture with a recominant vaccinia virus comprising a DNA sequence encoding said hemagglutinin, culturing said culture under conditions suitable to allow expression of the protein, and the isolation of the protein from the cell culture. Note the autoradiograph showing the immunoprecipitation of HA polypeptides on a polyacrylamide gel in Figure 4.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 22, 29, and 32 are rejected under 35 U.S.C. § 103 as being unpatentable over Smith et al., reference BT, or Paoletti et al., reference BJ, in view of Sofer et al. or Smith et al. (reference BS).

The important role of HBV as the etiological agent of both acute and late hepatitis in humans is well known in the art. Numerous laboratories have produced the highly immunogenic HBsAg to use as a human vaccine. Smith et al. and Paoletti et al. teach a method of producing HbSAg which comprises infecting a culture of eukaryotic cells with a recombinant vaccinia virus which comprises the DNA encoding HBsAg. For example, note Smith et al., Table 1. Sofer et al. broadly teach how to design optimal purification schemes using various purification techniques and Sofer et al. teach that HPLC methods have the ability to separate proteins which differ by as little as a single amino acid or that differ only in conformation. Smith et al. teach the standard techniques of immunoprecipitating a protein from a cell culture using an antibody specific for said protein and resolution of the protein on a polyacrylamide gel. Accordingly, in view of the important pharmaceutical role of the HBsAg and the teachings of Smith et al. and Paoletti et al. as to a method of producing HBsAg by infecting a culture of eucaryotic cells with a recombinant vaccinia virus encoding the HBsAg, the teachings of Sofer et al. and Smith et al. as to the standard methods in the art for protein isolation and purification and, absent an unexpected result, it would have been obvious to one of ordinary skill in the art to produce HBsAg using a recombinant vaccinia

virus expression system and to further isolate said antigen to use in a vaccine formulation. It would have been obvious to employ known materials for their known and expected results.

Claims 22, 24, and 25 are rejected under 35 U.S.C. § 103 as being unpatentable over Mackett et al., reference AX, in view of Sopher et al., Bonnerjea et al. or Smith et al. (reference BS).

Mackett et al. teach a method of producing thymidine kinase which comprises transfecting a culture of eucaryotic cells with a recombinant vaccinia virus which comprises the DNA sequence encoding thymidine kinase. Note Figure 4. Sofer et al. and Bonnerjea et al. broadly teach how to design optimal purification schemes using various purification techniques and Sofer et al. teach that HPLC methods have the ability to separate proteins which differ by as little as a single amino acid or that differ only in conformation. Smith et al. teach the standard techniques of immunoprecipitating a protein from a cell culture using an antibody specific for said protein and resolution of the protein on a polyacrylamide gel. Given the teachings of Mackett et al. as to a method of producing thymidine kinase which comprises transfecting a culture of eucaryotic host cells with a recombinant vaccinia virus comprising the DNA sequence encoding thymidine kinase and the teachings of Sofer et al., Bonnerjea et al. or Smith et al. as to the standard methods in the art for isolating and purifying proteins and, absent an unexpected result, it would have been obvious to one of ordinary skill in the art to produce and isolate thymidine kinase using the methods and

procedures taught by the references. It would have been obvious to employ known materials for their known and expected results.

Claims 22, 26, 27, and 30 are rejected under 35 U.S.C. § 103 as being unpatentable over Paoletti et al., reference BJ, in view of Bonnerjea et al., Sofer et al. or Smith et al. (reference BS).

Paoletti et al. teach a method of producing herpes simplex virus glycoprotein D which comprises transfecting a eucaryotic cell with a recombinant vaccinia virus comprising a DNA sequence encoding said glycoprotein. Sofer et al. and Bonnerjea et al. broadly teach how to design optimal purification schemes using various purification techniques and Sofer et al. teach that HPLC methods have the ability to separate proteins which differ by as little as a single amino acid or that differ only in conformation. Smith et al. teach the standard techniques of immunoprecipitating a protein from a cell culture using an antibody specific for said protein and resolution of the protein on a polyacrylamide gel. Given the teachings of Paoletti et al. as to a method of producing herpes simplex glycoprotein which comprises transfecting a culture of eucaryotic host cells with a recombinant vaccinia virus comprising the DNA sequence encoding herpes simplex glycoprotein and the teachings of Sofer et al., Bonnerjea et al., and Smith et al. as to the standard methods in the art for isolating and purifying proteins and, absent an unexpected result, it would have been obvious to one of ordinary skill in the art to produce and isolate herpes simplex glycoprotein using the

procedures taught by the references. It would have been obvious to employ known materials for their known and expected results.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Ellis whose telephone number is (703) 308-3990.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Ellis

JOAN ELLIS
PRIMARY EXAMINER
GROUP 180

J. Ellis, Ph.D.
February 14, 1995